REMARKS

Claims 1-26 are pending in this application. Claims 22 is amended herein to more clearly define the claimed subject matter. No new matter has been added by the amendments. Support for the amendments is found throughout the application and claims as originally filed. Applicants respectfully reserve the right to pursue any non-elected, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

It is submitted that the claims, herewith and as originally presented were in full compliance with the requirements of 35 U.S.C. § 112. The amendment of the claims, as presented herein, is not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, this amendment is made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendment should not give rise to any estoppel.

Reconsideration and withdrawal of the objections to and the rejections of this application in view of the amendments and remarks herewith, is respectfully requested, as the application is in condition for allowance.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 22-26 stand rejected as failing to adequately describe or reasonably enable the treatment or prevention of "any solid tumor or all proliferative disorders." Applicants respectfully disagree and traverse.

Furthermore, although Applicants strongly disagree with the Examiner's allegation that the specification is viewed as lacking enablement for prevention of any of the diseases recited, the pending claims have been amended to delete the term "or preventing," solely to expedite the prosecution of the present application, and without prejudice to Applicants' right to pursue them in one or more continuation, divisional or continuation-in-part applications. In view of these amendments and the following discussions, Applicants respectfully submit that the rejection should be withdrawn.

With regard to the methods of treatment of the present claims, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *U.S. v. Telectronics, Inc.,* 857 F.2d 778, 785 (Fed. Cir. 1988). The examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *Manual of Patent Examining Procedure* ("MPEP") § 2164.04 (citing *In re Wright,* 999 F.2d 1557, 1562 (Fed. Cir. 1993)).

Accordingly:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must be taken as being in compliance with the enablement requirement* ... unless there is a *reason to doubt the objective truth of the statements* contained therein which must be relied on for enabling support
>
> * * *
>
> It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

Id. (emphases added).

Applicants respectfully submit that whether or not the scope of a claim is broad is irrelevant to the assessment of the enablement of the claim. The question is whether those skilled in the art would have been able to make and use the claimed invention based on the disclosure. *(See U.S. v. Telectronics, Inc.,* at 785).

Applicants respectfully submit that the pending claims are enabled because the specification "contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented." *Id.*

For example, the specification teaches that the compounds of the present invention are useful in treating hyperproliferative disorders which "include but are not limited to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukemias" (Page 125, lines 19-22). The specification further describes various specific tumors which can be treated (Page 125, line 23 – Page 126, line 22). Similarly, it is disclosed that the claimed compounds can be prepared by synthetic procedures described in Schemes 1-3 and in Examples 1-365. Therefore, it is clear that a sufficient guidance is provided in the specification so as to allow those of ordinary skill in the art to make and use the claimed invention, as required by 35 U.S.C. § 112, first paragraph.

Nonetheless, the Examiner further alleges that there is insufficient "evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host," and thus that one skilled in the art would have to undergo an undue amount of experimentation in consideration of factors 1-6 set forth in *In re Wands*. Applicants respectfully disagree with the allegations.

To the extent that the IC_{50} data provided herein are *in vitro,* Applicants point out that to demonstrate utility, Applicants need only show that any given compound is pharmacologically active *in vitro. See Cross v. Iizuka*, 753 F.2d 1040, 1051 (Fed. Cir. 1985) ("Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility.) (citations omitted). Further, "[i]f a statement of utility in the specification contains ... a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated," the enablement requirement is satisfied.

Manual of Patent Examination and Procedure § 2164.01(c) (citing, *inter alia, In re Brana, 51* F.3d 1560, 1566 (Fed. Cir. 1993)).

Moreover, "[a]n *in vitro* or *in vivo* animal model in the specification, in effect, constitutes a 'working example' if the example 'correlates' with a disclosed or claimed method" (MPEP § 2164.02). Explaining further, MPEP § 2164.02 states:

> "[I]f the state of the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition."

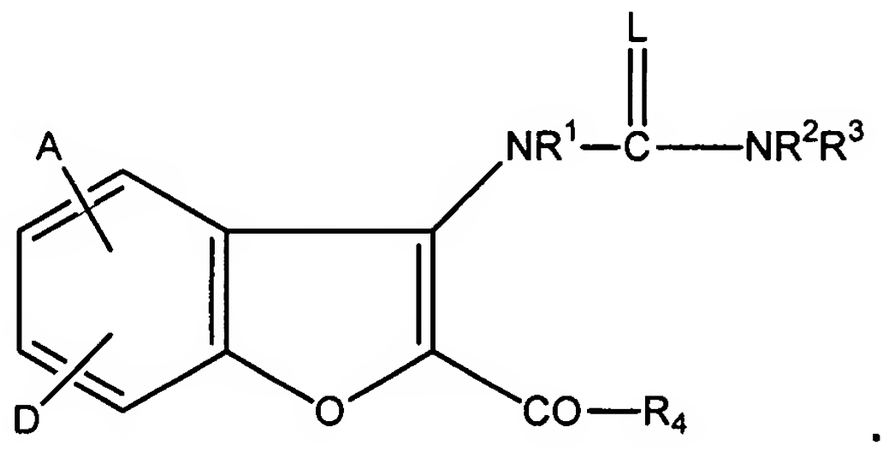
Finally, MPEP § 2164.02 also recognizes that "a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence" (quoting *Cross v. Iizuka,* 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)).

In view of the foregoing, it is clear that sufficient guidance is provided in the specification so as to allow those of ordinary skill in the art to make and use the claimed invention. Indeed, the claimed invention is directed to the use of obtainable compounds. The skilled artisan can readily determine the IC_{50} for any of the compounds encompassed by the claims by using the methods described in the specification, which can be readily used to determine that a synthesized compound is useful in the treatment of the diseases recited in the claims. Moreover, the determination by a physician as to whether a claimed compound is effective in treating a recited disease in a given patient is a type of determination that is <u>always</u> made by physicians for <u>every</u> pharmaceutical. Indeed, the determination is a <u>routine</u> one that every physician is prepared to make, and which requires little or no effort. Therefore, Applicants respectfully submit that one reasonably skilled in the art could make or use the invention as claimed without undue experimentation.

In sum, Applicants respectfully submit that: (1) the specification provides sufficient information and guidance to those of ordinary skill in the art to make and use the claimed invention; (2) the Examiner did not provide any factual or legal basis to doubt that the claims are enabled; and (3) to the extent any experimentation is necessary, such experimentation is not undue. Therefore, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn

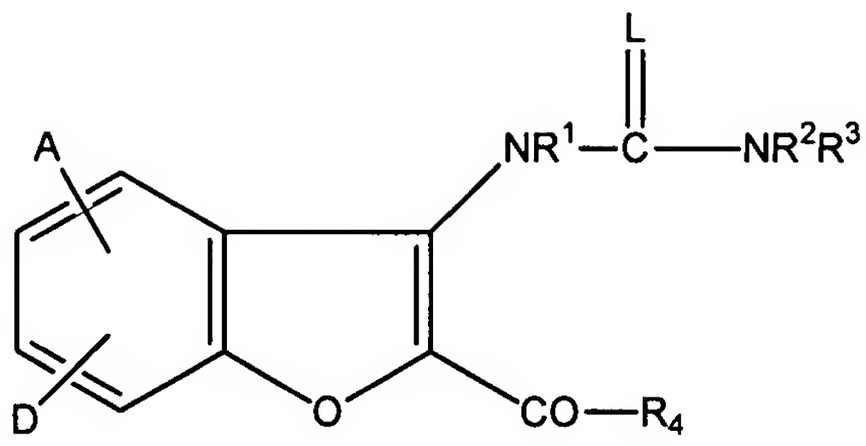
Rejections under 35 U.S.C. § 102

Claims 1-2, 4-6, 8-9, 14-18, 20, 22-23, and 25-26 stand rejected under 35 USC §102(b) as being anticipated by European Patent No. EP 0 779 291 (European Equivalent of U.S. Patent No. 5,922,740) to Branulich et al. ("Branulich I"). Branulich I teaches heterocyclylcarbonyl substituted benzofuranyl-ureas of the formula:



Applicants respectfully traverse the rejection. The Examiner references compounds of table 1 as anticipatory of the instant claims. None of the compounds disclosed by Branulich I disclose the limitation that R_4 of the presently claimed compounds be piperonyl, optionally substituted heterocycle, or optionally substituted phenyl or naphthyl. Indeed, All of the compounds of table 1 of Branulich I have either hydrogen, methoxy, methyl, trifluoromethyl, nitro, or cyano in the Y position (represented as A or D above but as Y in the tables – *See*, Columns 20-26 of the '740 Patent). As such, Branulich I does not teach or disclose all of the claimed limitations.

Claims 1-2, 4-6, 8-9, 14-18, 20, 22-23, and 25-26 stand rejected under 35 USC §102(b) as being anticipated by European Patent No. EP 0 731 099 to Branulich et al. ("Branulich II"). Branulich II teaches N-(3-benzofuranyl)urea derivatives of the formula:



Applicants respectfully traverse the rejection. The Examiner references compounds of tables I-V as anticipatory of the instant claims. None of the compounds disclosed by Branulich II disclose the limitation that R_4 of the presently claimed compounds be piperonyl, optionally substituted heterocycle, or optionally substituted phenyl or naphthyl. Indeed, even the generic description of substituents in Branulich II – represented as D in Table I, hydrogen in Table II, and Y in Tables III and IV – does not encompass this limitation. As such, Branulich II does not teach or disclose all of the claimed limitations.

As neither Branulich I nor Branulich II anticipates the instant invention, Applicants respectfully request reconsideration and withdrawal of the rejections.

Rejections under 35 U.S.C. § 103

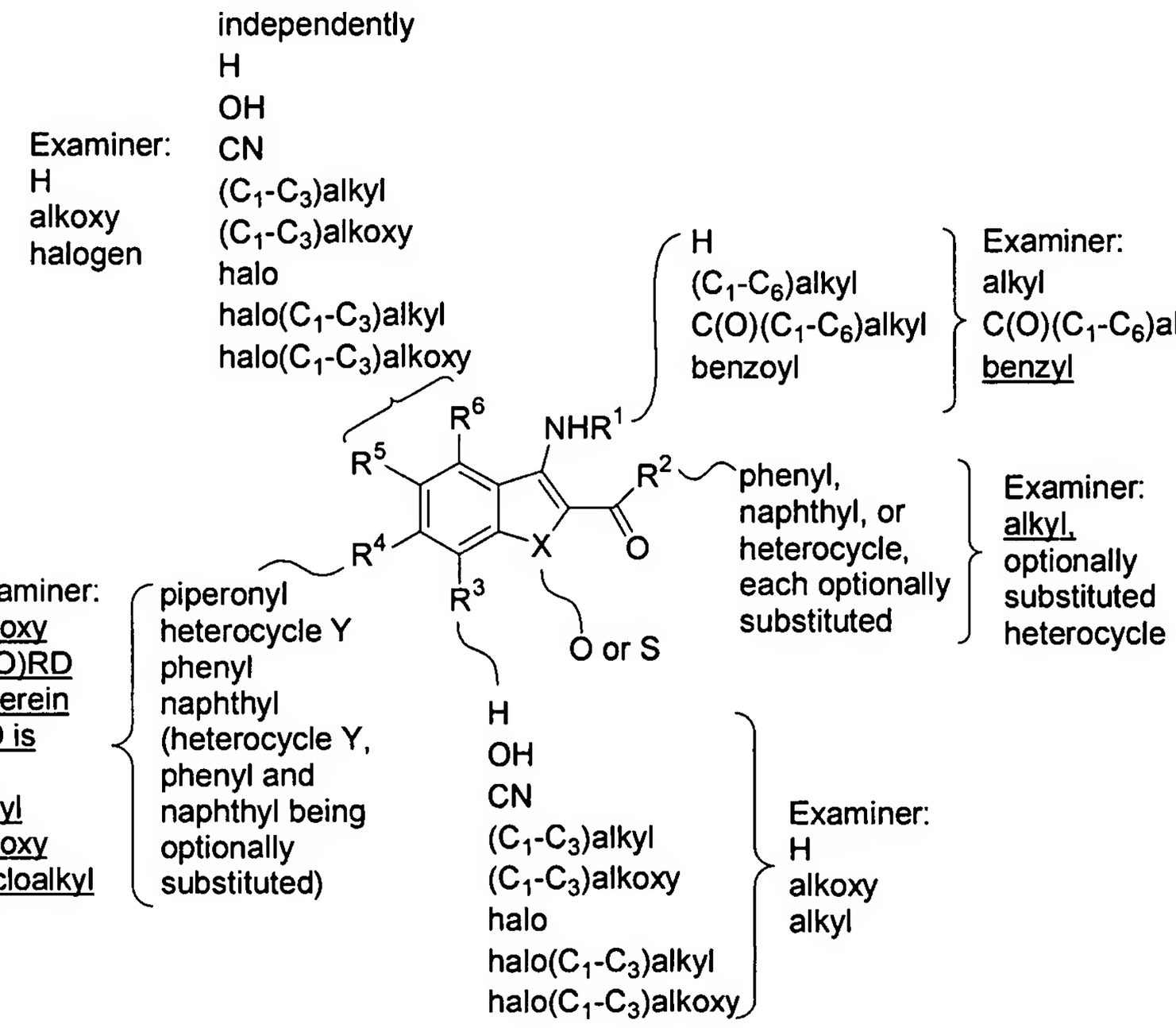
Claims 1, 3, 11, 14, and 15 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over McKinnon et al. *Canadian J. Chem* (1984) Vol 62(8) p. 1580 – 1584 ("McKinnon") and Boeshagen et al. *Justus Liebigs Annelen der Chemie* (1972), Vol. 764, p 58-68 ("Boeshagen"), individually.

Claims 1-2, 4-6, 8-9, and 16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Harwalkar et al. *Indian J. Het. Chem.* (1994), Vol 3(4), p. 247-257 ("Harwalkar") and European Patent No. 0 755 934 to Osswald et al ("Osswald"), individually.

Claims 1-6, 8-12, and 14-21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Radl et al *Collection of Czechoslovak Chem. Commu.* (2000), Vol 65(7), p 1093-1088 ("Radl").

Claims 1-2, 4-6, 8-9, 14-18, 20, 22-23, and 25-26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Branulich II, described above.

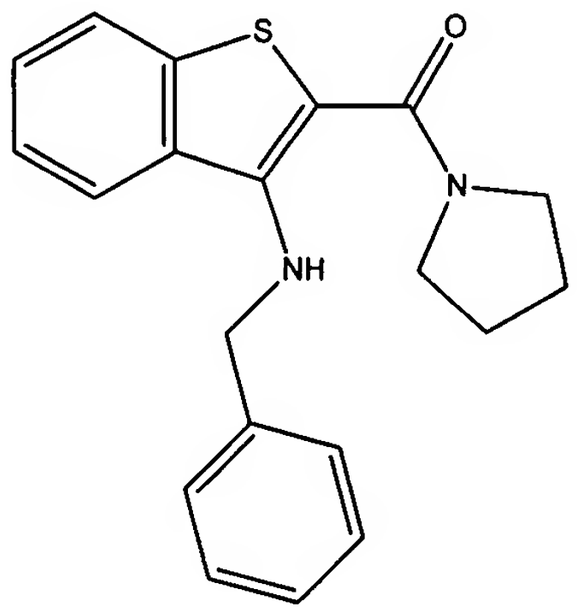
Applicants respectfully disagree and traverse these rejections. As an initial matter the Examiner alleges that Applicants claim "compounds of formula (I), composition and method of use for treating ... a hyperproliferative disorder... [wherein] X is O or S, R1 is alkyl, C(O)(C1-6)alkyl or benzyl; R2 is alkyl, optionally substituted heterocycle; R3 is H, alkoxy or alkyl; R4 is alkoxy, C(O)RD, RD is H, alkyl, alkoxy, or cycloalkyl; R5 and R6 are H, alkoxy or halogen". Applicants respectfully disagree. As can readily be seen in the Listing of the Claims presented herein, the presently claimed compounds are as described below – the Examiner's characterization is also included for ease of comparison.



Particular attention is directed to the fact that R^4 is not "alkoxy or C(O)RD", but is instead ***piperonyl, optionally substituted heterocycle, or optionally substituted phenyl or naphthyl***.

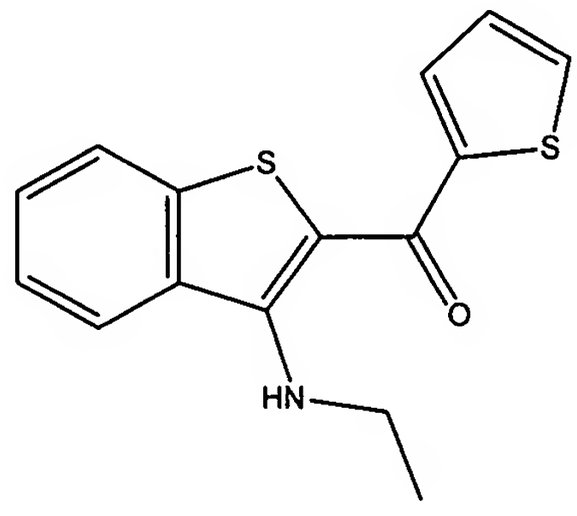
To properly determine a prima facie case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P § 2142. This is important as "impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art." *Id.* Three basic criteria must then be met: first, there must be some suggestion or motivation to modify or combine the cited references; second, there must be a reasonable expectation of success; and third, the prior art references must teach or suggest all the claim limitations. M.P.E.P §2143. With regard to the first criterion, the "mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." M.P.E.P §2143.01 (citing *In re Mills*, 916 F.3d 690 (Fed. Cir. 1990)). "Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render claim obvious." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Teleflex*, [*Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1333-34 (Fed. Cir. 2002)]. The issue is whether substantial evidence supports the judgment (under the clear and convincing evidence standard) that a person having ordinary skill in the art would not have been motivated to replace the [prior art] combination ... with [the claimed combination.]" *Abbott Laboratories v. Syntron Bioresearch, Inc.*, 334 F.3d 1343, (Fed. Cir. 2003).

With regards to McKinnon, the Examiner alleges that McKinnon teaches a compound having the formula:



It is noted that the Examiner has relied solely on the CAPLUS computer generated database listing in making this allegation and has not shown the compound in the reference itself. The Examiner further alleges that the only difference between the instant invention and the compound described in the CAPLUS database listing, is that "alkyl is claimed at position R4 instead of H" and that "one of ordinary skill in the art would have known to replace alkyl with H at the time the instant invention was made....[as] H and alkyl are equivalents." Without conceding the validity of the Examiner's allegations regarding the teaching of the structure or the equivalency of H and alkyl, Applicants respectfully draw the Examiners attention to the fact that the instant application does not claim alkyl at the R^4 position. Furthermore, the instant application does not claim benzyl at R1 but instead benzoyl. Instead, all of the claimed compounds require R^4 to be piperonyl, optionally substituted heterocycle, or optionally substituted phenyl or naphthyl.

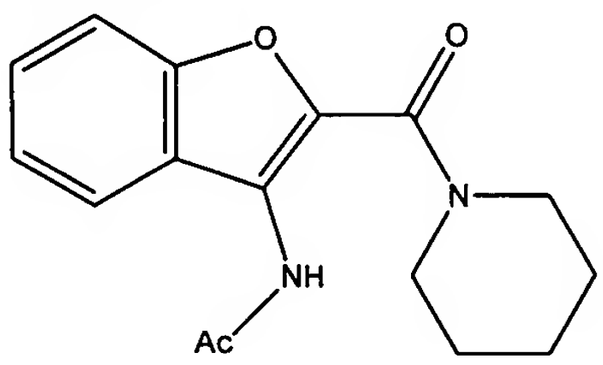
With regards to Boeshagen, the Examiner alleges that Boeshagen teaches a compound having the formula:



It is noted that the Examiner has relied solely on the CAPLUS computer generated database listing in making this allegation and has not shown the compound

in the reference itself. The Examiner further alleges that the only difference between the instant invention and the compound described in the CAPLUS database listing, is that "alkyl is claimed at position R4 instead of H" and that "one of ordinary skill in the art would have known to replace alkyl with H at the time the instant invention was made....[as] H and alkyl are equivalents." Without conceding the validity of the Examiner's allegations regarding the teaching of the structure or the equivalency of H and alkyl, Applicants respectfully draw the Examiners attention to the fact that the instant application does not claim alkyl at the R^4 position. Instead, all of the claimed compounds require R^4 to be piperonyl, optionally substituted heterocycle, or optionally substituted phenyl or naphthyl.

With regards to Harwalkar, the Examiner alleges that Harwalkar teaches compounds having the formula:



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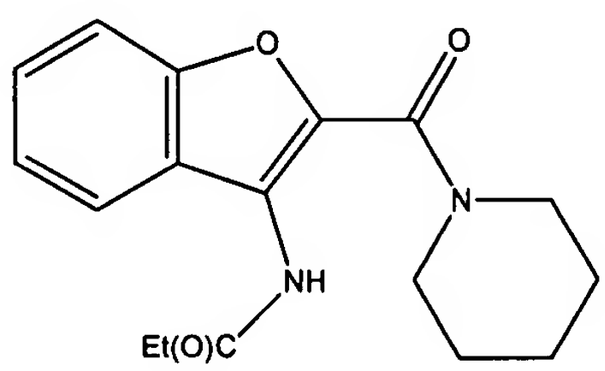

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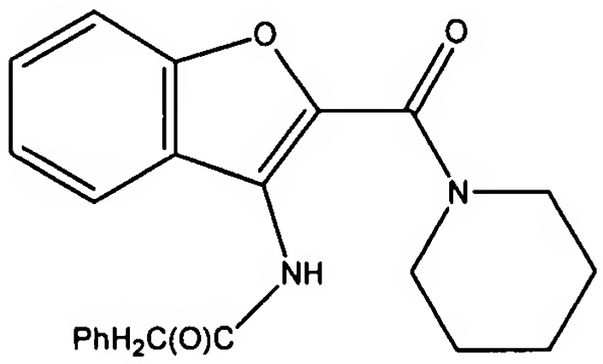
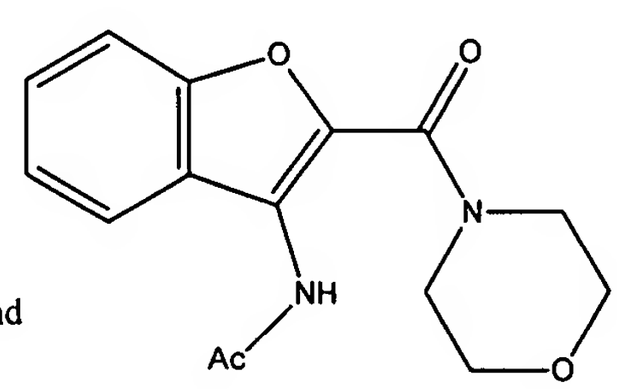


, and


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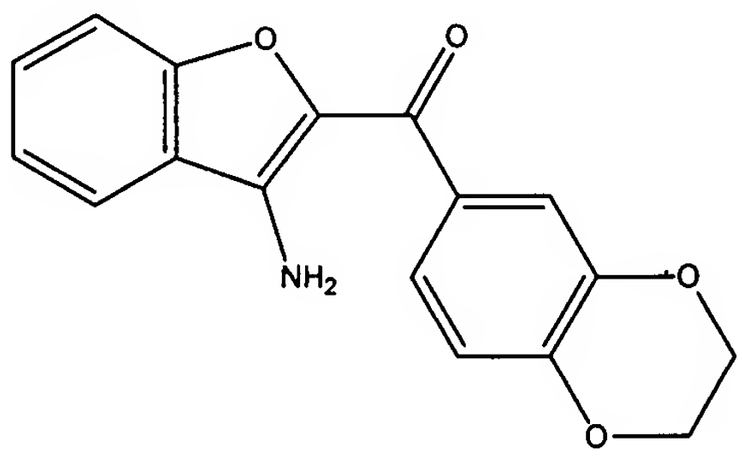
It is noted that the Examiner has relied solely on the CAPLUS computer generated database listing in making this allegation and has not shown the compound in the reference itself. The Examiner further alleges that the only difference between the instant invention and the compounds described in the CAPLUS database listing, is that "alkyl is claimed at position R4 instead of H" and that "one of ordinary skill in the art would have known to replace alkyl with H at the time the instant invention was

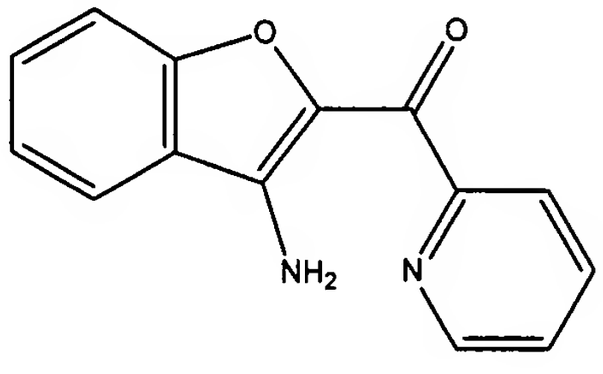
made....[as] H and alkyl are equivalents." Without conceding the validity of the Examiner's allegations regarding the teaching of the structures or the equivalency of H and alkyl, Applicants respectfully draw the Examiners attention to the fact that the instant application does not claim alkyl at the R^4 position. Furthermore, the instant application does not claim benzyl at R1 but instead benzoyl. Instead, all of the claimed compounds require R^4 to be piperonyl, optionally substituted heterocycle, or optionally substituted phenyl or naphthyl.

With regards to Osswald, the Examiner alleges that Osswald teaches a compound having the formula:



It is noted that the Examiner has relied solely on the CAPLUS computer generated database listing in making this allegation and has not shown the compound in the reference itself. The Examiner further alleges that the only difference between the instant invention and the compound described in the CAPLUS database listing, is that "alkyl is claimed at position R4 instead of H" and that "one of ordinary skill in the art would have known to replace alkyl with H at the time the instant invention was made....[as] H and alkyl are equivalents." Without conceding the validity of the Examiner's allegations regarding the teaching of the structure or the equivalency of H and alkyl, Applicants respectfully draw the Examiners attention to the fact that the instant application does not claim alkyl at the R^4 position. Instead, all of the claimed compounds require R^4 to be piperonyl, optionally substituted heterocycle, or optionally substituted phenyl or naphthyl.

With regards to Radl, the Examiner alleges that Radl teaches compounds having the formula:



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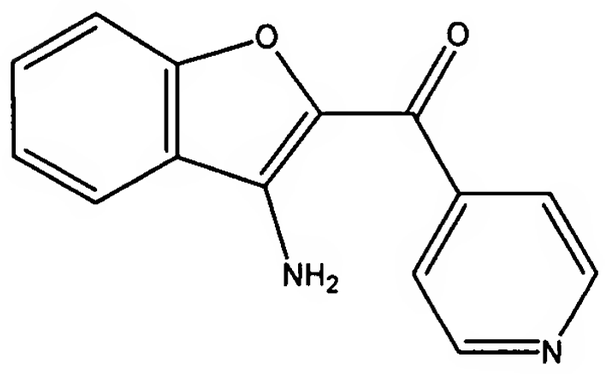

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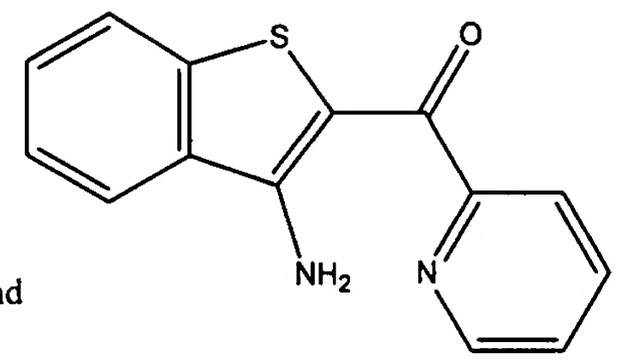

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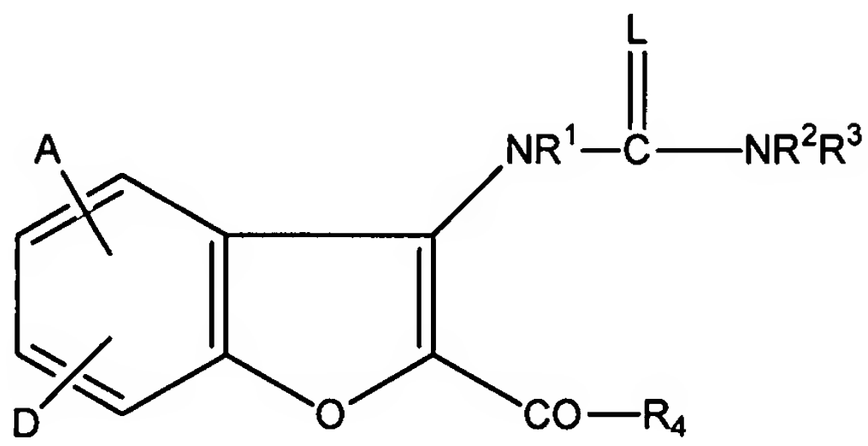
It is noted that the Examiner has relied solely on the CAPLUS computer generated database listing in making this allegation and has not shown the compound in the reference itself. The Examiner further alleges that the only difference between the instant invention and the compound described in the CAPLUS database listing, is that "alkyl is claimed at position R4 instead of H" and that "one of ordinary skill in the art would have known to replace alkyl with H at the time the instant invention was made....[as] H and alkyl are equivalents." Without conceding the validity of the Examiner's allegations regarding the teaching of the structures or the equivalency of H and alkyl, Applicants respectfully draw the Examiners attention to the fact that the instant application does not claim alkyl at the R^4 position. Instead, all of the claimed compounds require R^4 to be piperonyl, optionally substituted heterocycle, or optionally substituted phenyl or naphthyl.

With regards to Branulich II, as described above, Branulich II teaches N-(3-benzofuranyl)urea derivatives of formula I:



The Examiner alleges that the only difference between the instant invention and the compounds described is that "alkyl is claimed at position R4 instead of H" and that "one of ordinary skill in the art would have known to replace alkyl with H at the time the instant invention was made....[as] H and alkyl are equivalents." Without conceding the validity of the Examiner's allegations regarding the equivalency of H and alkyl, Applicants respectfully draw the Examiners attention to the fact that the instant application does not claim alkyl at the R^4 position. Instead, all of the claimed compounds require R^4 to be piperonyl, optionally substituted heterocycle, or optionally substituted phenyl or naphthyl.

Indeed, with regard to all of the cited art, Applicants respectfully assert that one of skill in the art would not recognize the piperonyl, optionally substituted heterocycle, or optionally substituted phenyl or naphthyl claimed at the R^4 position as an equivalent to hydrogen as the steric and chemical properties of these substitutents would be expected to be vastly different from those of hydrogen. One of skill in the art, would have lacked the motivation to modify the compounds of McKinnin, Boeshagen, Harwalkar, Osswald, Radl or Branulich II at the R^4 position to arrive at the instant compounds.

Accordingly, reconsideration and withdrawal of all rejections under 35 U.S.C. § 103 are respectfully requested.

CONCLUSION

In view of the amendments and remarks made herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105.

Respectfully submitted,

Date: April 25, 2007

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